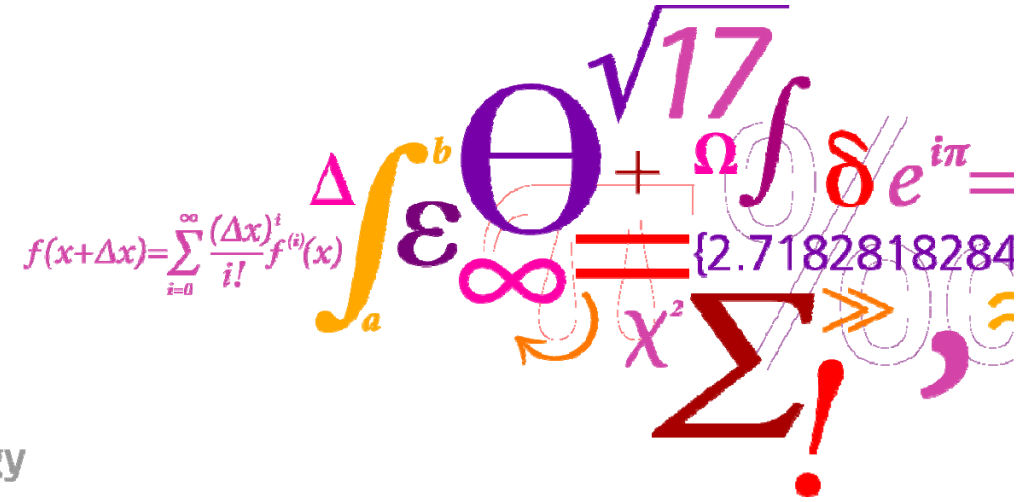
Educating students to boost innovation

.....creating value for society

.....technology-based entrepreneurship



Rolf Henrik Berg

18 September 2013

DTU Nanotech
Department of Micro- and Nanotechnology

WHY innovation?

...a growth engine

- Creates **new** jobs: Start-up companies
- **Maintains** jobs: Strengthening the competitive position of existing companies

Innovation is not a choice

.....it is really a matter of

Focus of today's talk

- **The innovative research environment**
  - University-industry collaboration is key
  - Searching luck, permission to fail

- **The "go it alone" decision – technology entrepreneurs**
  - We need more – what is missing?

- **Patents – important commercial instruments**
  - Lessons learned

WHAT is innovation?

…one of the most widespread buzzwords

Definition(s)

- OECD: ”Product development”
- DTU: **Research-based** renewal of an external party’s product, technology or process – aimed at creating added value in companies and society

…definition probably reflects where you are

…must result in (salable) product or service

HOW do you stimulate innovation?

…..perhaps easy to define – but in practice?

Begins with: The ***good idea*** (or discovery)

- Can come from anywhere
- Often very simple
- Often requires more … advanced technology/knowledge

The innovative ***environment***

…..perhaps more relevant to define

- Since everybody can get a good idea
- About the ***probability*** of getting a good idea
- Can you create an environment which generates the good idea?

What does *not* work?

…..innovation ”killers”

- Easily goes wrong if you try to manage it too much
- **A**dministrators and micro management too early in the process easily results in innovation in a ”straitjacket”

….it is about being excited about something

….straitjacket OK when you ”smell blood”…now innovation is fun

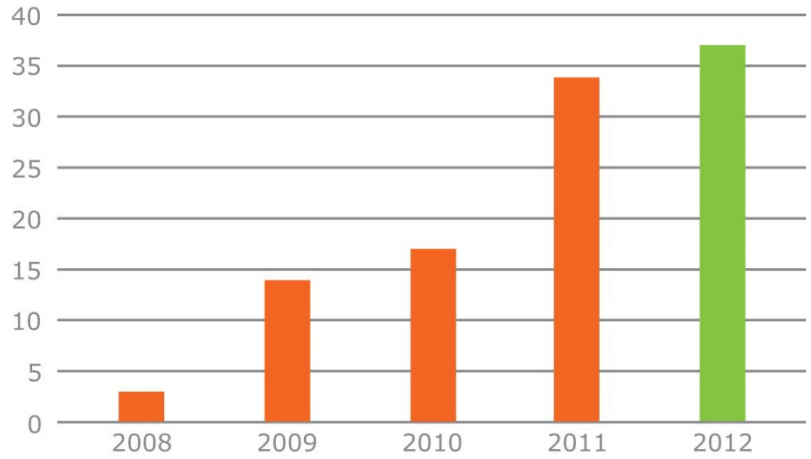
You know who to talk to….

…your good idea …… ***perhaps it is useful!***

…the sooner the better

Keep it simple…

Invention disclosures (DTU Nanotech)



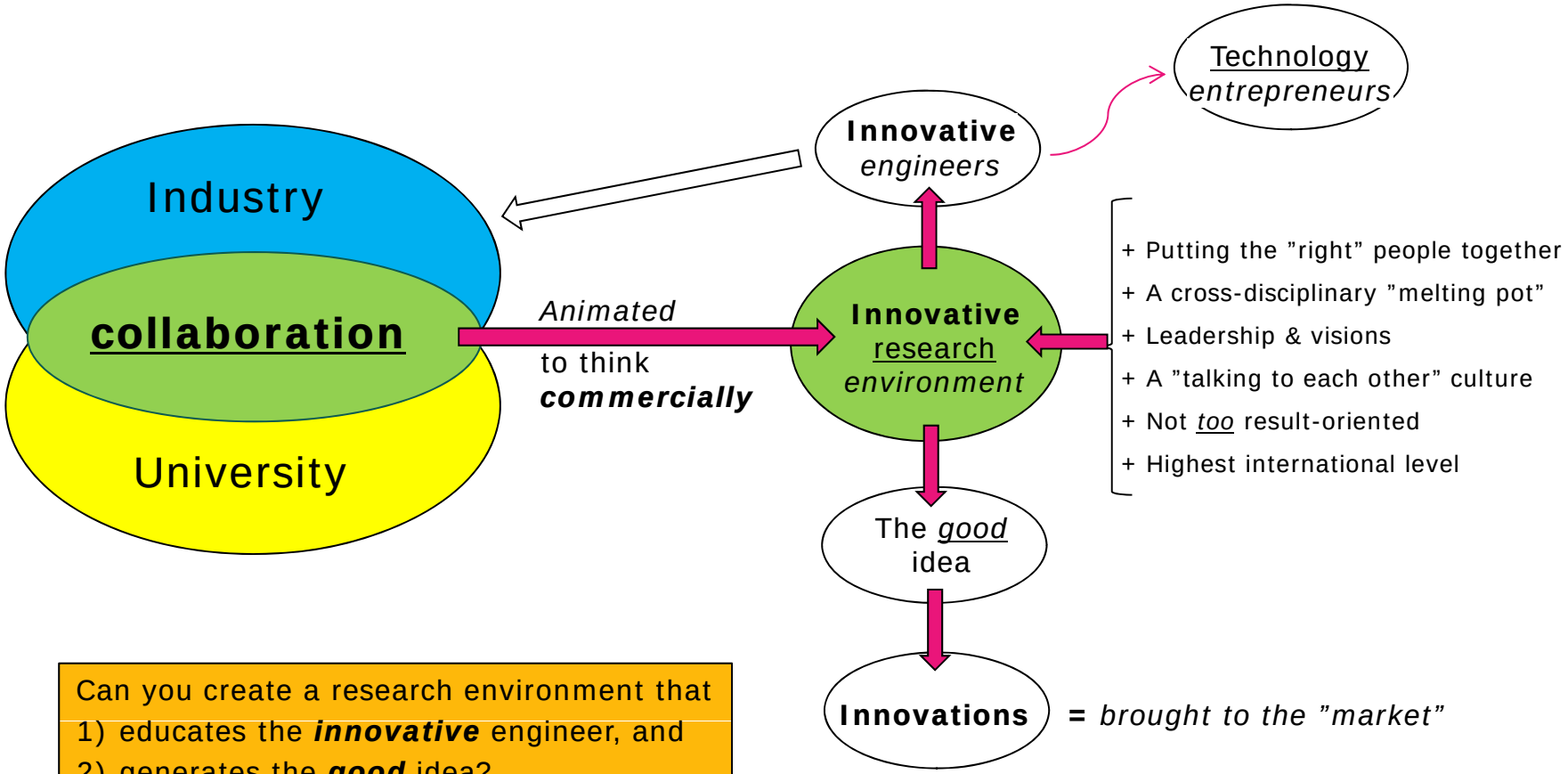
The ***innovative*** research environment

.....HOW?

- Putting (the ”right”) people together
- Create a cross-disciplinary ”melting pot” of strong basic scientific skills/competences
- Building a ”talking to each other” culture
- Leadership & visions
- Not *too* result-oriented research, but ***animated*** to think commercially

The *innovative* research environment

…industry-university collaboration is key

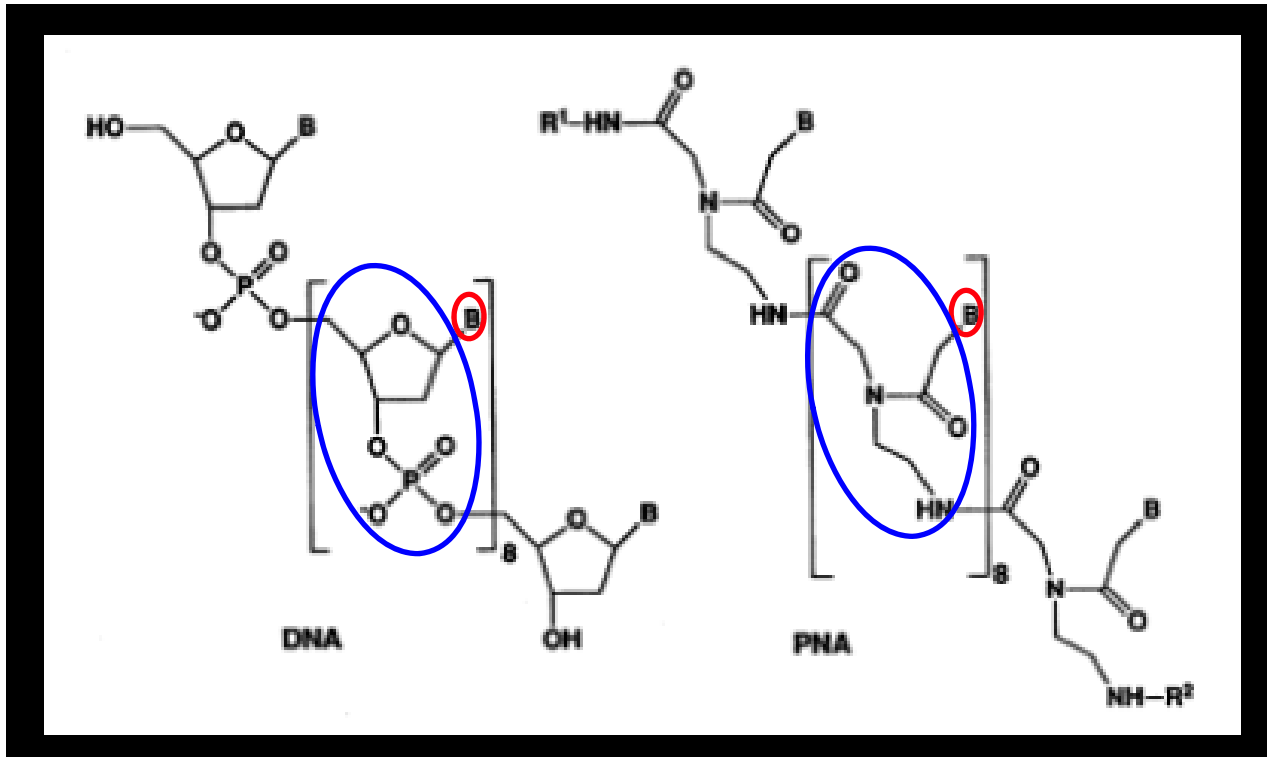


Can you create a research environment that
1) educates the ***innovative*** engineer, and
2) generates the ***good*** idea?

It is about the **probability**

PNA - Discovery of artificial DNA

...almost by accident

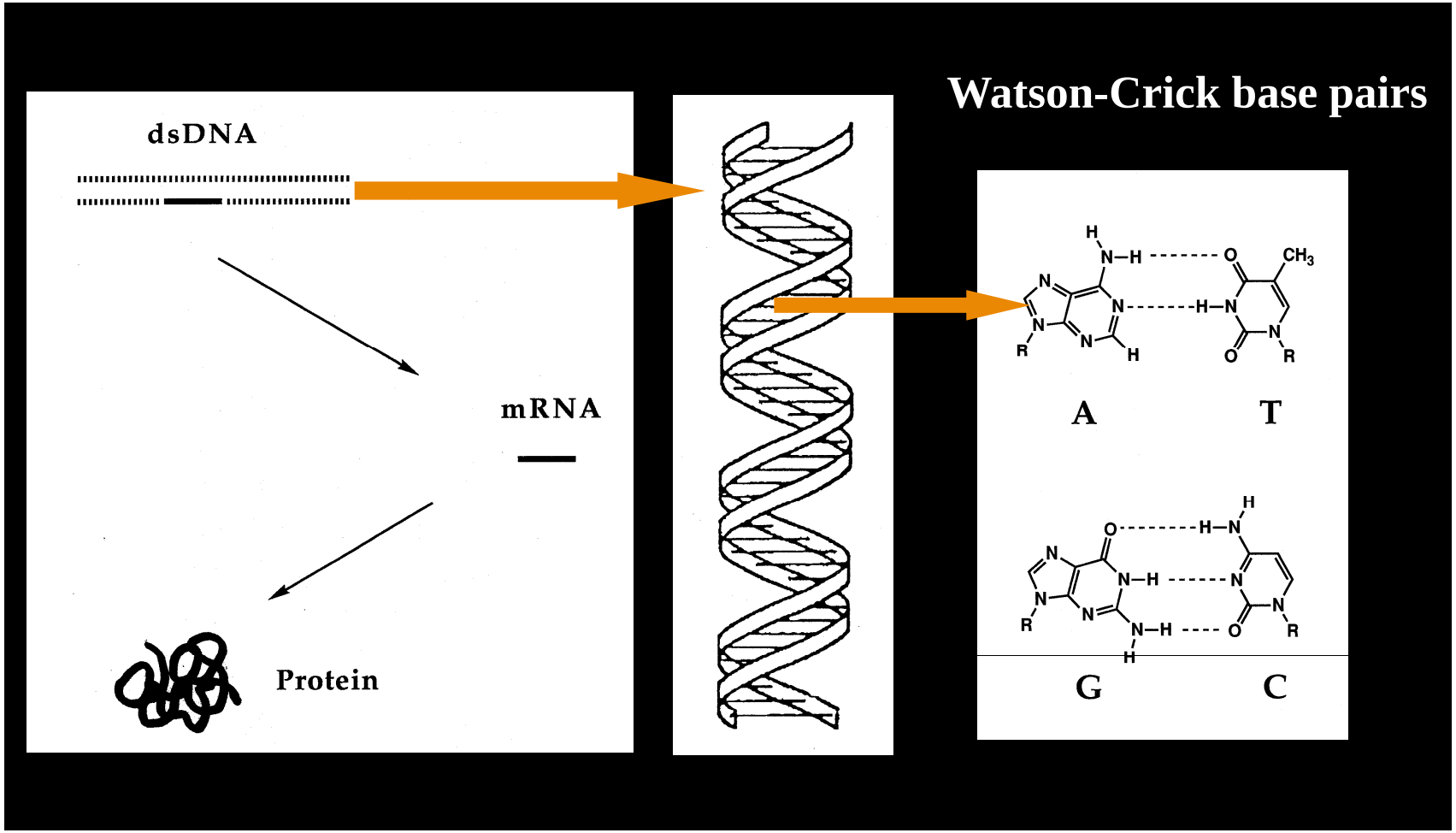


University of Copenhagen
Michael Egholm
Peter E. Nielsen
Ole Buchardt

Risø National Laboratory
Rolf Henrik Berg

Motivation

...to obtain some level of "control" of gene expression

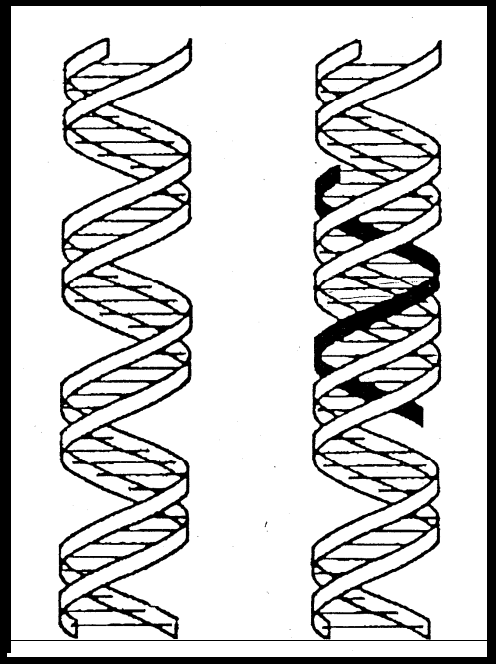


The plan

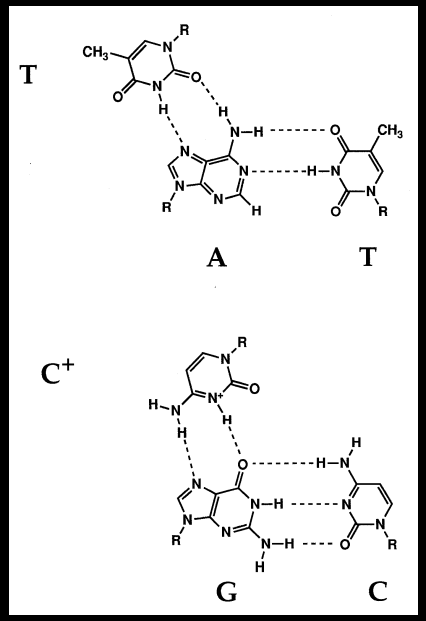
...to find a structure that showed some hint that it worked

Our wildest dream

If PNA could form a triplex with DNA

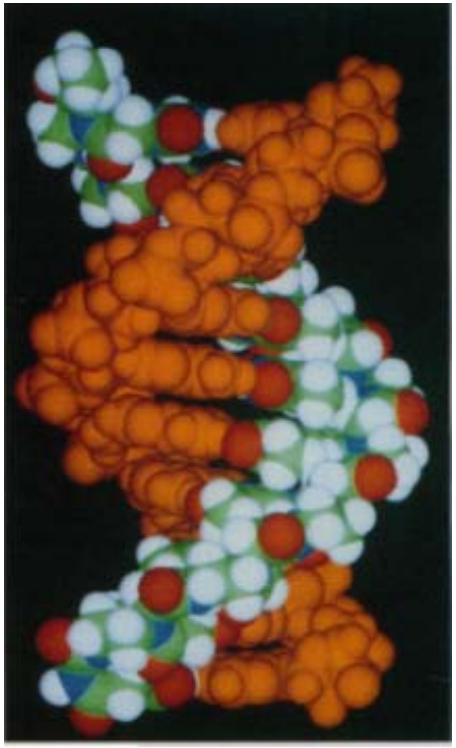


Hoogsteen base pairs



...and then spend the next 20-30 years optimizing the structure

BINGO!!



Science (1991)

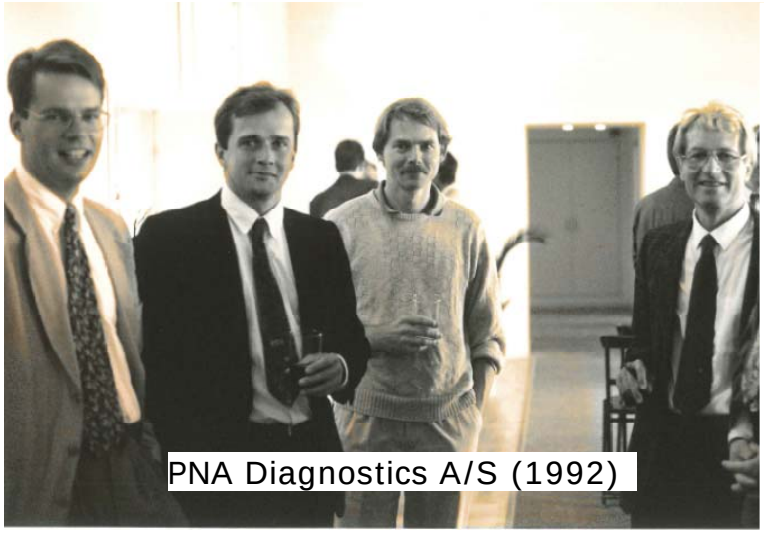
"The new molecules [PNA], brainchildren of chemists Michael Egholm, Peter Nielsen, Ole Buchardt, and Rolf Berg ... ***has spurred a flurry of activity at biotech companies****"*

- Editorial, ***Science*** (1993)

Case: PNA – discovery of artificial DNA

*BIG surprise!...**almost** by accident*

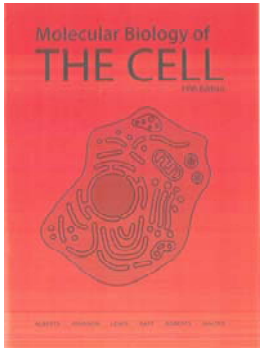
Science (1991)



PNA Diagnostics A/S (1992)

University of Copenhagen
Michael Egholm
Peter E. Nielsen
Ole Buchardt

Risø National Lab.
Rolf Henrik Berg



>2,500 scientific articles, >25,000 US patents (is./pend.),
7 start-ups, and products on the market (including FDA clearance)

Electronics?

NEWS FOCUS

NANOTECHNOLOGY

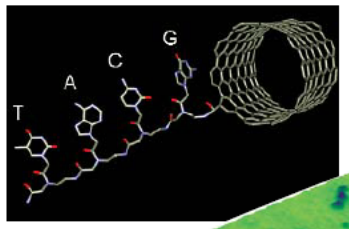
Biology Offers Nanotechs A Helping Hand

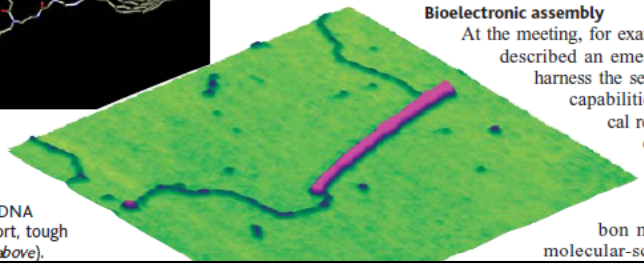
Rather than building tiny devices atom by atom, nanoscientists are raiding biology's molecular toolbox in hopes of revolutionizing sensors, medical diagnostics, and electronics

BOSTON, MASSACHUSETTS—When it comes to nanotechnology, physicists, chemists, and materials scientists can't hold a candle to the simplest bacteria. Billions of years of evolution have outfitted organisms of all stripes with a wealth of nanomachines—from the information-storage medium of DNA to the proteins that capture sunlight and copy DNA during cell division. Early nanotech visionaries dreamed of crafting their own versions of nanomachinery and even went so far as to draw up molecular specs for tiny gears and motors. But at the Materials Research Society meeting here earlier this month,* it was clear that as nanotechnology begins to leave its infancy and find its feet, most nanobuilders are looking to biology not just for inspiration but also a little practical help.

In labs around the globe, researchers are working to marry biology and nanotechnology, fusing nanomanufacturing tools. "There are a lot of ideas emerging right now," says Günter Schmid, a chemist at the University of Essen, Germany.

One of the biggest drivers behind nanotechnology's enthusiasm for biological systems revolves around an organism's impressive ability to manufacture complex molecules such as DNA and proteins with atomic precision. Chemists create molecules up to hundreds of atoms in size without too much trouble, controlling the position of every atom. But beyond that, traditional synthetic schemes become unwieldy and too inef-





Welded. In this micrograph, a carbon nanotube (purple) trails DNA anchored by short, tough PNA molecules (*above*).

Complex biological machines also show an uncanny knack for homing in on and binding to molecular targets amid a sea of other molecules. "Biomachinery is a powerful way of bringing organization into a system," notes Keith Williams, a physicist and nanotech expert at the Delft Institute of Technology in the Netherlands. By contrast, engineered nanosized objects such as carbon nanotubes and tiny spherical metal and semiconducting particles lack any guidance mechanism. That makes it extremely difficult to put those tubes and particles where you want them to go. "As materials become so small, they become difficult to handle with traditional methods such as lithography," the technique used to pattern computer chips, says Williams.

As a result, until researchers learn to construct complex nanostructures from the ground up, they have little choice but to become small-time thieves. "Instead of trying to build [nanostructures] from scratch, let's just steal them from biology," says Jacob Schmidt, a bioengineer at the University of California, Los Angeles. A handful of nanotech research groups has been perpetrating such theft in recent years, Mirkin and others say, but now the nano field is in the midst of a kleptomania epidemic.

Bioelectronic assembly

At the meeting, for example, Williams described an emerging effort to harness the selective binding capabilities of a chemical relative of DNA called peptide nucleic acid (PNA) to assemble carbon nanotubes into molecular-scale electronic

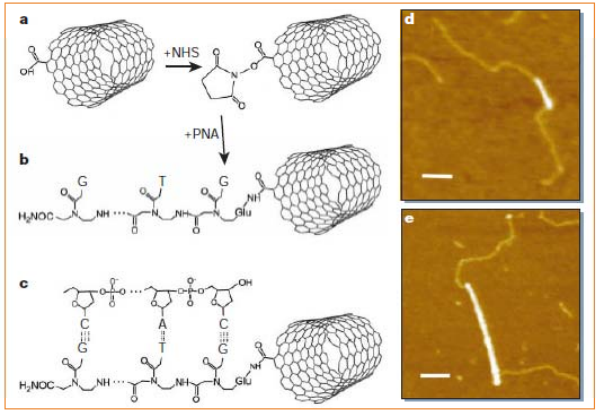
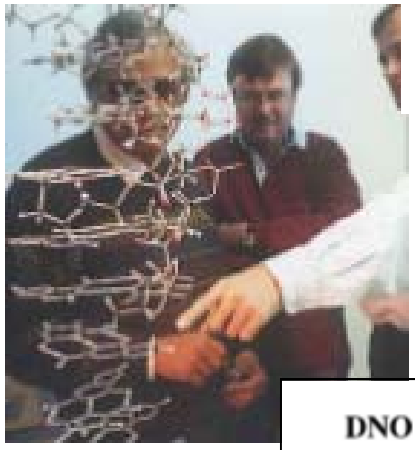


Figure 1 Attachment of DNA to carbon nanotubes. **a, b,** *N*-hydroxysuccinimide (NHS) esters formed on carboxylated, single-walled carbon nanotubes (SWNTs) are displaced by peptide nucleic acid (PNA), forming an amide linkage. **c,** A DNA fragment with a single-stranded, 'sticky' end hybridizes by Watson–Crick base-pairing to the PNA–SWNT. **d, e,** Atomic-force microscope (TappingMode) images of PNA–SWNTs. SWNTs appear as bright lines; the paler strands represent bound DNA. Scale bars: 100 nm; nanotube diameters: **d**, 0.9 nm; **e**, 1.6 nm.

NATURE | VOL 420 | 19/26 DECEMBER 2002 | www.nature.com/nature

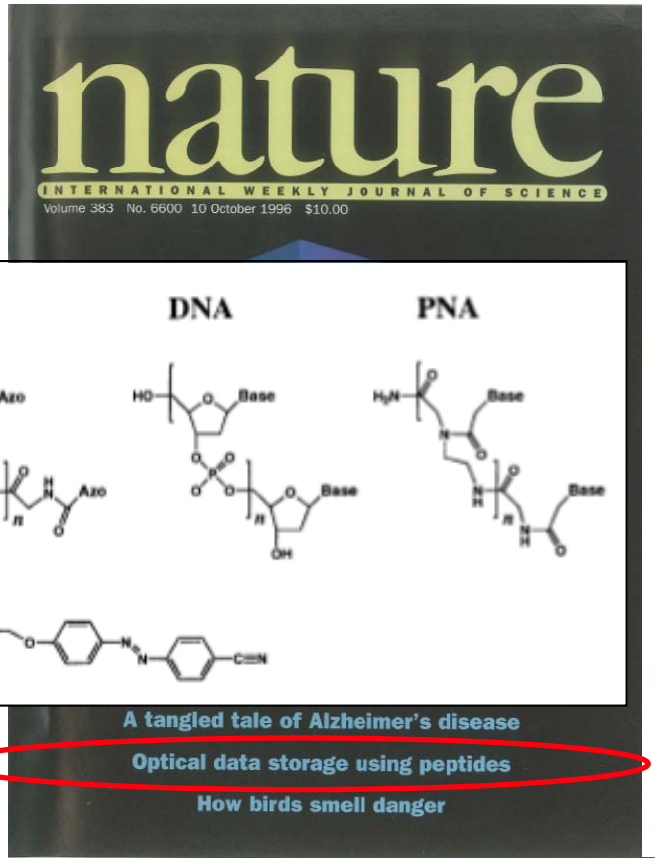
Photonics?



Peptide oligomers for holographic data storage

Rolf H. Berg, Søren Hvilsted & P. S. Ramanujam

Risø National Laboratory, DK-4000 Roskilde, Denmark



NEWS AND VIEWS

But Berg *et al.*[3] add a new dimension to the tailoring of organic molecules for photonic applications. They show that by using supramolecular architectures from biology, the performance of such materials can be improved. By linking the functional molecules to a peptide-like backbone, they can impose helical stacking in a manner similar to that in DNA. The planar azo-benzene molecules orientate themselves until their planes are in a direction perpendicular to the light field, as they would do singly, but being coordinated by the backbone they cannot rotate

FIG. 2 Dennis Gabor, reconstructed from a 1-mm^2 peptide hologram. Gabor invented holography in 1948 (ref. 5).

PNA - what happened?

…an innovative research environment?

Research enviroment

- *Fruitful* research environment
- *Visionary* leader
- Close collaborations with *industry*

The good idea

- Went for something interesting
- Driven by: *perhaps it could be used*
- BINGO! – lucky, accidentally, it was great

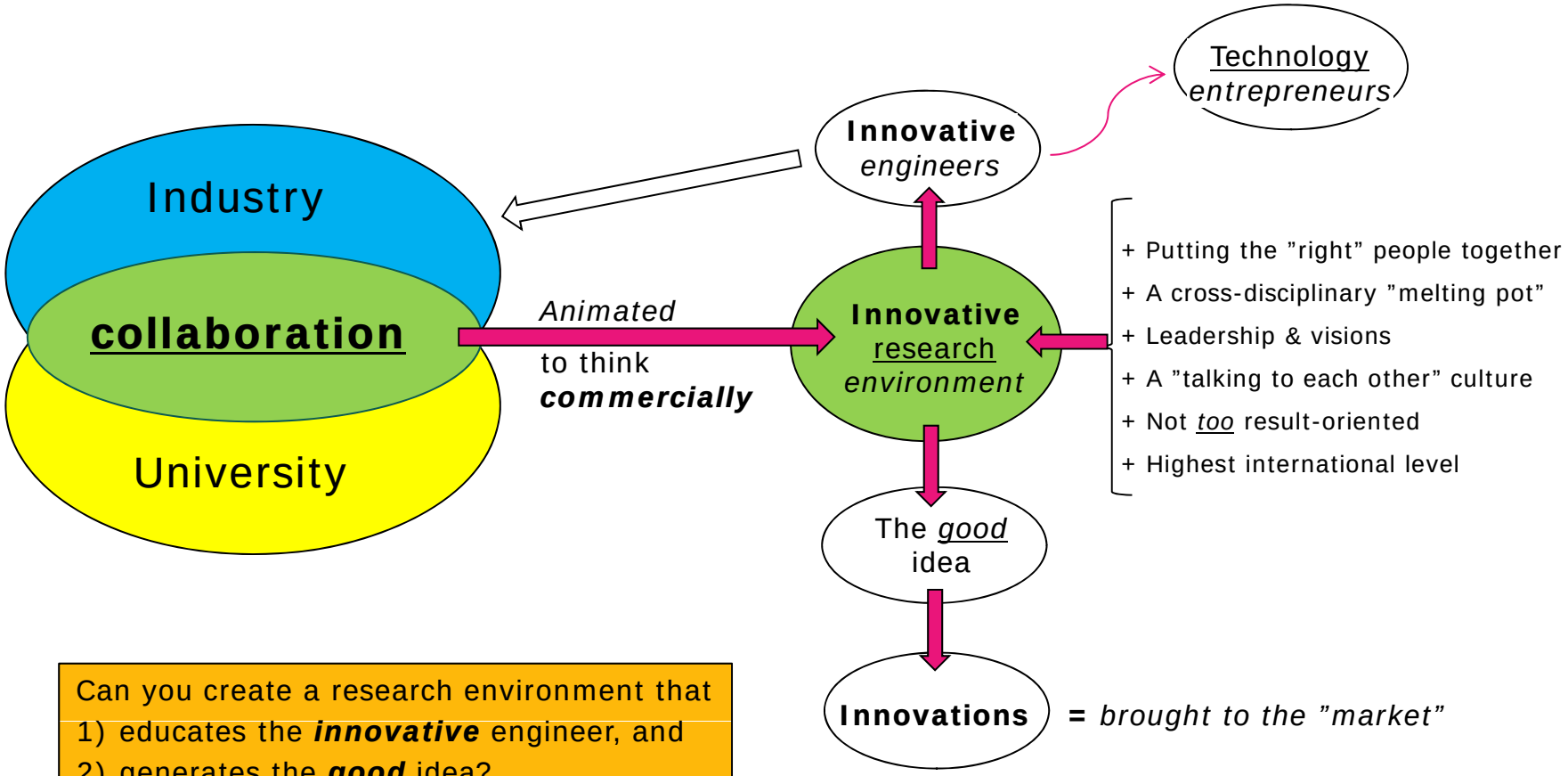
High ambition

&

Searching luck

The *innovative* research environment

…industry-university collaboration is key



Can you create a research environment that
1) educates the ***innovative*** engineer, and
2) generates the ***good*** idea?

It is about the **probability**

HTF: NanoPlast – a technological platform

Vision

Revolutionize the way you provide functionality to ”daily life” plastic products – by nanotechnology

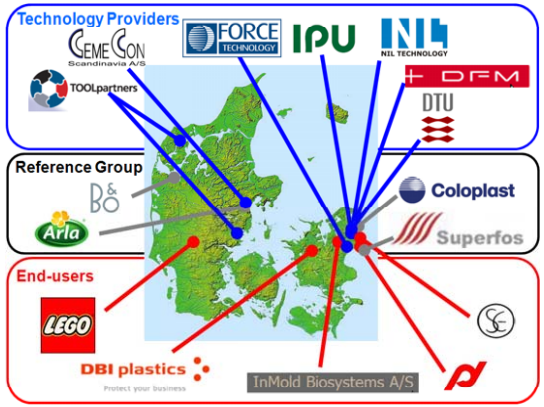
Enhancement of competitive edge for Danish injection moulding industry

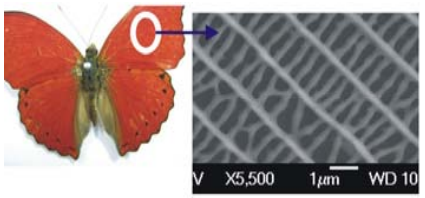
Budget

91 MDKK (50 MDKK from HTF)

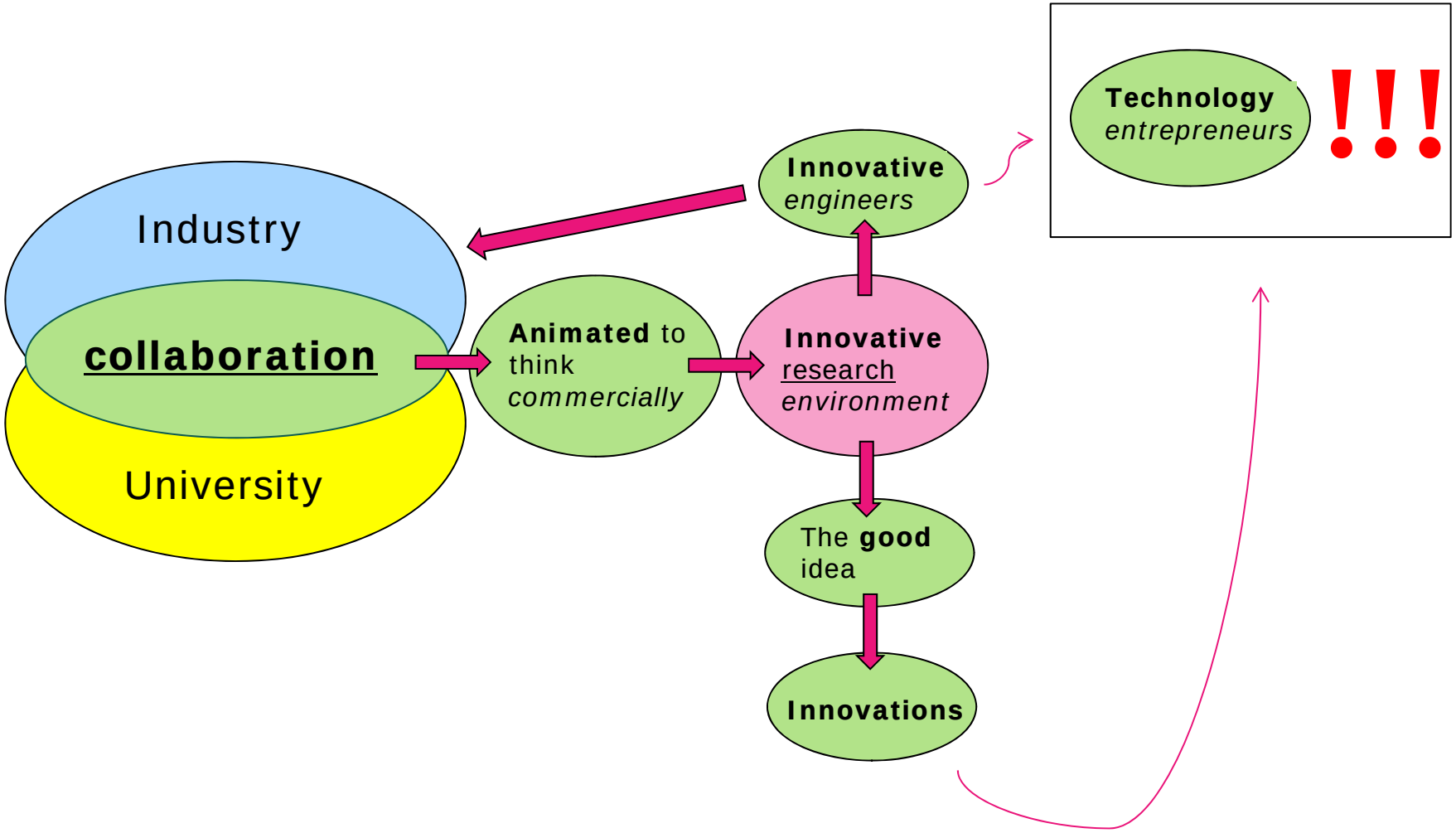
Platform Leader

DTU Nanotech





Technology entrepreneurs



Creating the initial phase

…turning on entrepreneurial …

… ”fiery souls”

Examples from DTU Nanotech

Venture Cup 2013

Owerall Winner

Venture Cup 2012

Category Winner

Venture Cup 2011

Owerall Winner

Start-ups

- 16 start-ups have emerged from DTU Nanotech over the past 12 years

cantion
Cantilever based biosensor

CHEMPAQ microinstruments
Blood cells analysis

Thorion Diagnostics

New
Nanovi A/S

ionas
Planar light circuits

HYMITE
Packaging

NIL TECHNOLOGY
Stamps for nanoimprint technology

sophion
Patch Clamp Analysis

SMB
Polymer microstructures

SERSTECH
Surface Enhanced Raman Spectroscopy

Quantum Wise
Atomic-scale modeling solutions

INAGEN
Treatments for intracellular parasitic diseases

CAPRES A/S
COPENHAGEN APPLIED RESEARCH
Four point probe

Dentofit / Aproxi ApS

BLACK SILICON SOLAR

Silmeco ApS

We need more - what is missing?

- What is driving ”real” entrepreneurs/co-founders?
- Special challenges for **technology** entrepreneurs?
- Could the ”go it alone” decision be made more attractive?

Getting people to do this

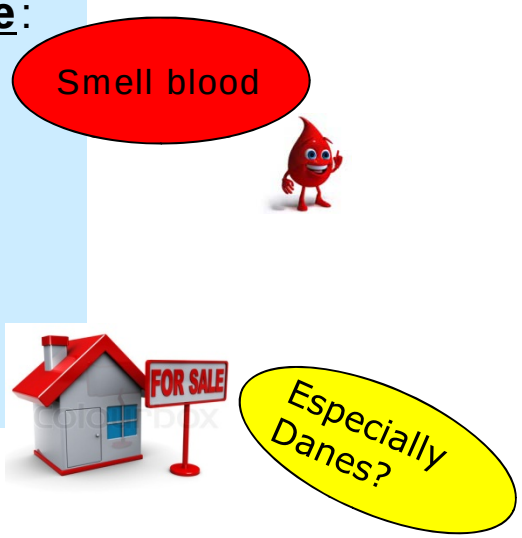
…what are the drivers?

1. They must be able to see an **upside**:

   - that they can make some money

&

2. That they do not risk being **ruined**.



…simple behavior

We live in an ”employee culture”

...OK, yes it is difficult to say:

”Now I start a company!”

BUT: Special challenge in <u>TECHNOLOGY</u> start-ups

Even you have the ”entrepreneurial DNA”

*- **<u>in practice</u>**, there is another big problem: **<u>MONEY!</u>***

It easily costs DKK 10M to develop a product

It is expensive!

What to do in the initial phase?

*…if you want to be a "**real**" entrepreneur?*

In **control** until "product stage"

Your are **prepared** to:

- Work 24/7
- "Live on a stone"

All-in, but NOT **financially**

But you **don't** want to:

- Take a loan in your parents' house (high-risk)
- Be an employee hired by investors
  - *– because you are diluted, and not in control*

You need to ”buy yourself time”

…for example, in order to:

- Establish the Company
- Understand the Market
- Learn book-keeping
- Make a ”bird’s nest” model
- Write a business plan
- Make the first contact to a company
  - *– a potential customer*
- Try making a development agreement with a customer
  - *– **customer-funded** financing*

Learn something and get something clarified

Can easily take two years

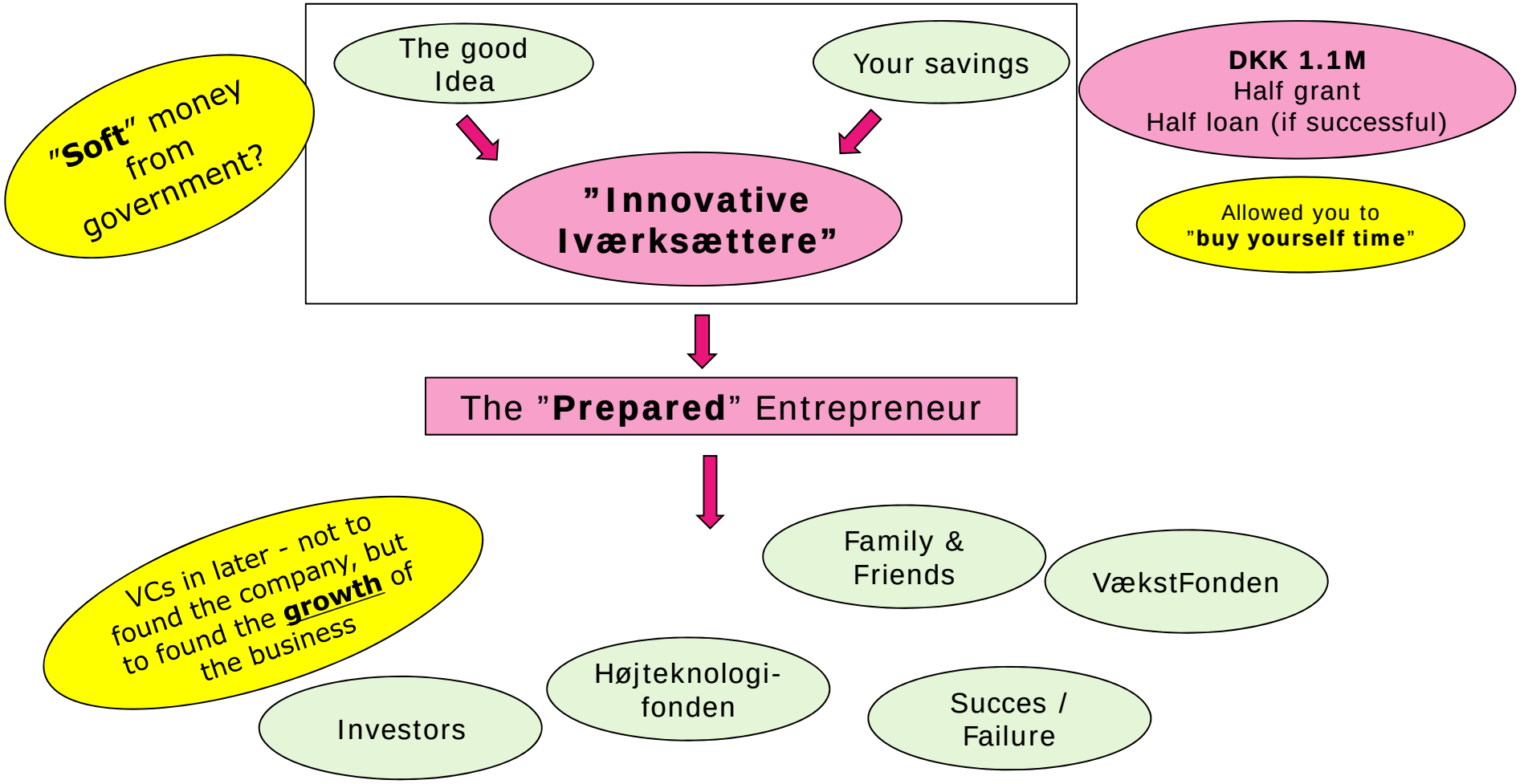
HOW??

Perhaps

Successful

Relaunch of an alternative "Danish" model?!

*… in style with the "**Innovative Iværksættere**" programme in the 90'es*



…think you be surprised how many would ”come out” based on DTU inventions

Some pitfalls

Patents – lessons learned

Why patents?.... expensive

- Protection of an invention often required before investing in product development (e.g. millions of US dollars)
- Grants the patent owner(s) the right to exclude others from ”make, use and sell” products based on the invention
- The patent owner(s) can *license* ”make, use and sell” rights under the patent

Note that:

A patent is a right granted on a country-by-country basis

The PNA story

1991 – PNA priority application filed 24 May

1991 – First preliminary (”T”) public disclosure 17 Jun

1991 – First exclusive license granted

1991 – *Science* paper (”T”) published 6 Dec

1992 – PNA Diagnostics A/S

1992 – More exclusive licenses granted

...so far so good

27 Nov 1992.....A little worried

Glaxo *Science* paper:

”A” works!

Antisense and Antigene Properties of Peptide Nucleic Acids

Jeffery C. Hanvey, Nancy J. Peffer, John E. Bisi, Stephen A. Thomson, Rodolfo Cadilla, John A. Josey, Daniel J. Ricca, C. Fred Hassman, Michele A. Bonham, Karin G. Au, Stephen G. Carter, David A. Bruckenstein, Ann L. Boyd, Stewart A. Noble, Lee E. Babiss*

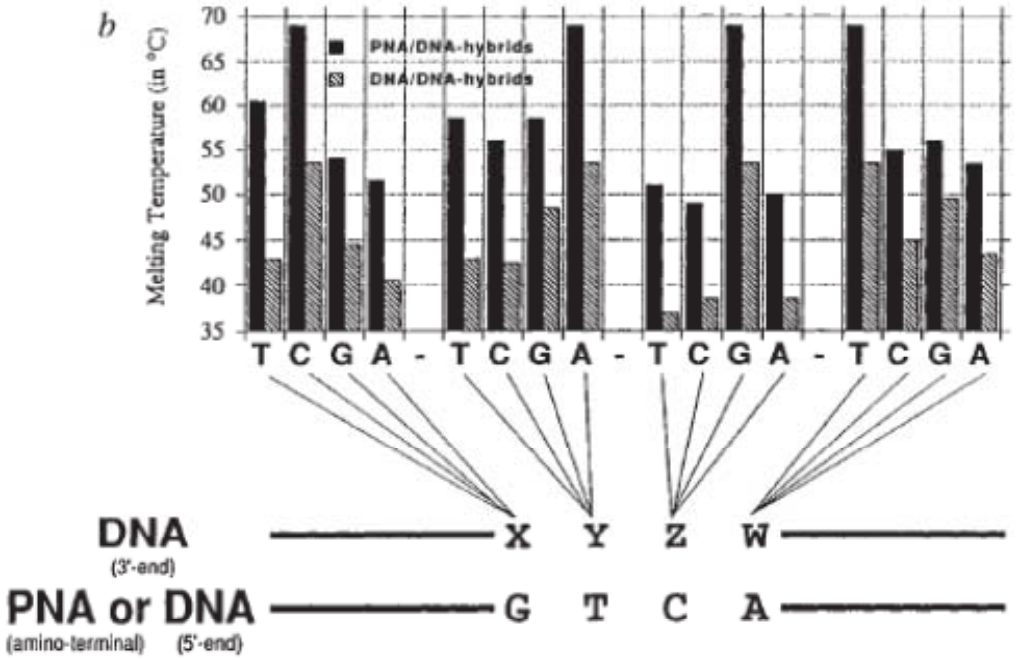
Peptide nucleic acids (PNAs) are polyamide oligomers that can strand invade duplex DNA, causing displacement of one DNA strand and formation of a D-loop. Binding of either a T_{10} PNA or a mixed sequence 15-mer PNA to the transcribed strand of a G-free transcription cassette caused 90 to 100 percent site-specific termination of pol II transcription elongation. When a T_{10} PNA was bound on the nontranscribed strand, site-specific inhibition never exceeded 50 percent. Binding of PNAs to RNA resulted in site-specific termination of both reverse transcription and in vitro translation, precisely at the position of the PNA · RNA heteroduplex. Nuclear microinjection of cells constitutively expressing SV40 large T antigen (T Ag) with either a 15-mer or 20-mer PNA targeted to the T Ag messenger RNA suppressed T Ag expression. This effect was specific in that there was no reduction in β-galactosidase expression from a coinjected expression vector and no inhibition of T Ag expression after microinjection of a 10-mer PNA.

Sequence-specific binding of oligodeoxynucleotides (ODNs) to RNA or in the major groove of duplex DNA through triple-helix formation provides a way to modulate gene expression (*1*, *2*). Although the potential of ODNs as antisense or antigene agents is actively being explored, the problems associated with creating in vivo bioefficacy and-maintaining binding specificity and affinity are formidable.

J. C. Hanvey, N. J. Peffer, J. E. Bisi, S. A. Thomson, R. Cadilla, J. A. Josey, D. J. Ricca, C. F. Hassman, M. A. Bonham, K. G. Au, S. G. Carter, D. A. Bruckenstein, S. A. Noble, L. E. Babiss, Departments of Cell Biology and Medicinal Chemistry, Glaxo Inc. Research Institute, 5 Moore Drive, Research Triangle Park, NC 27709. A. L. Boyd, Department of Biology, Hood College, Frederick, MD 21701.

*To whom correspondence should be addressed.

Fortunately, ”ATCG” *Nature* paper accepted!



Egholm M *et al.* ***Nature*** (1993)

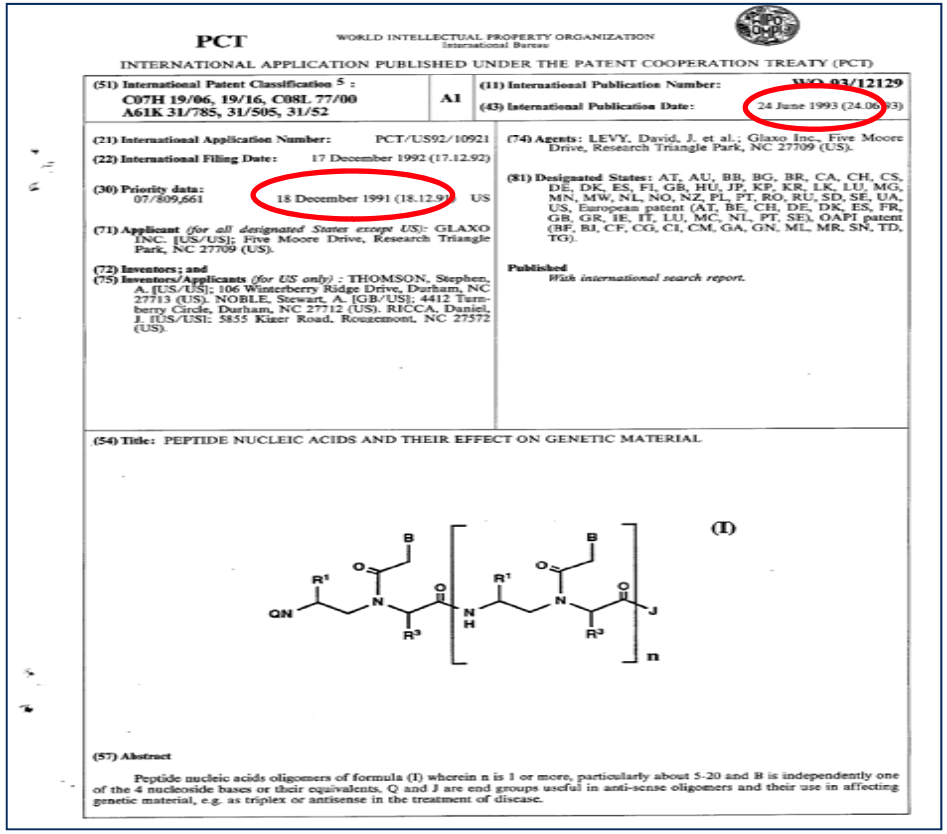
BUT…24 Jun 1993…Extremely worried!!

Glaxo *PCT application*:

”A” reduced to practice

Priority date:

18 Dec 1991!!



PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07H 19/06, 19/16, C08L 77/00 A61K 31/785, 31/505, 31/52 — A1

(11) International Publication Number: WO 93/12129

(43) International Publication Date: 24 June 1993 (24.06.93)

(21) International Application Number: PCT/US92/10921

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(71) Applicant (for all designated States except US): GLAXO INC. [US/US]; Five Moore Drive, Research Triangle Park, NC 27709 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only) : THOMSON, Stephen, A. [US/US]; 106 Winterberry Ridge Drive, Durham, NC 27713 (US). NOBLE, Stewart, A. [GB/US]; 4412 Turnberry Circle, Durham, NC 27712 (US). RICCA, Daniel, J. [US/US]; 5855 Kiger Road, Rougemont, NC 27572 (US).

(74) Agents: LEVY, David, J. et al.; Glaxo Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US).

(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.

(54) Title: PEPTIDE NUCLEIC ACIDS AND THEIR EFFECT ON GENETIC MATERIAL

(I)

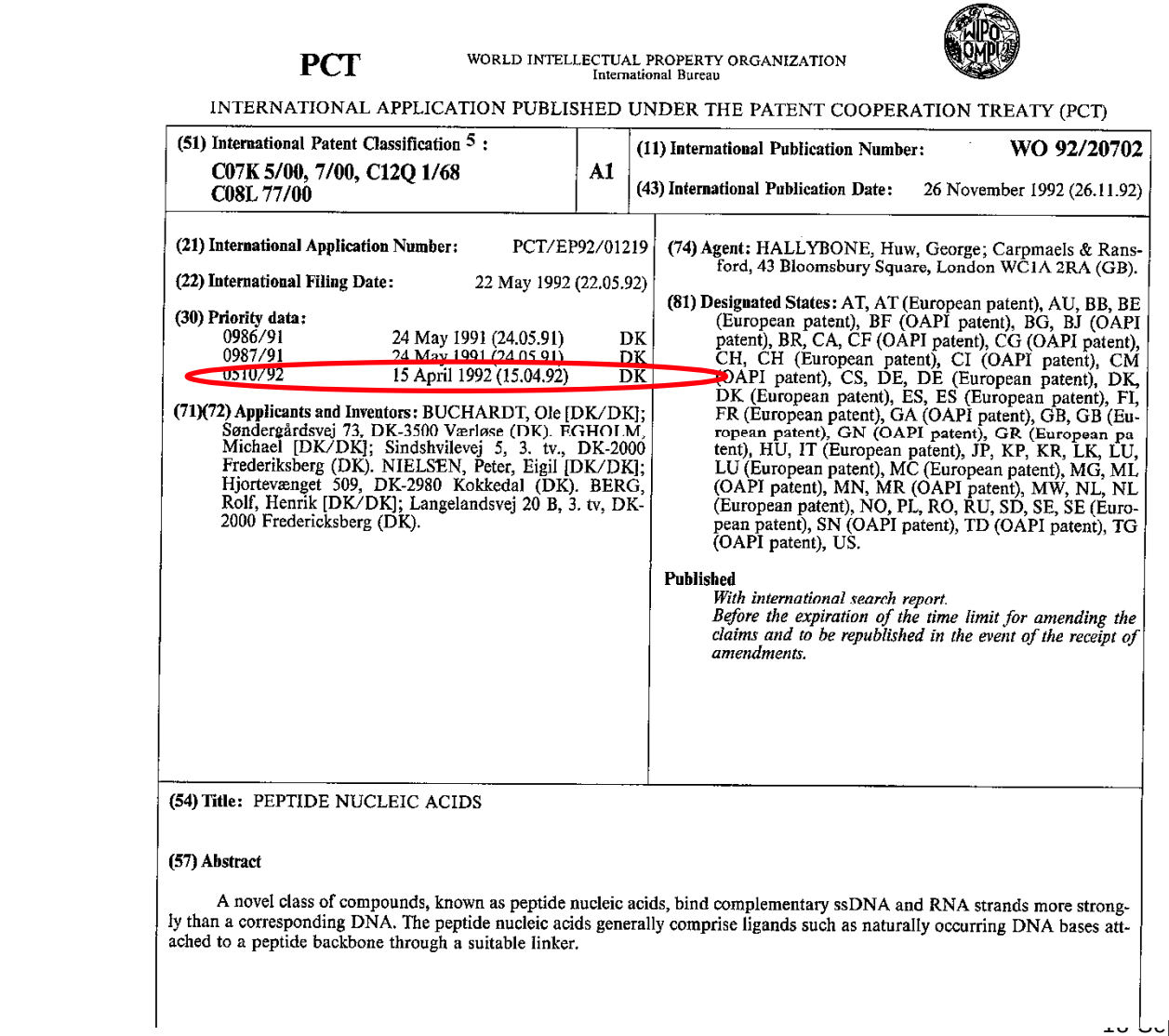
(57) Abstract

Peptide nucleic acids oligomers of formula (I) wherein n is 1 or more, particularly about 5-20 and B is independently one of the 4 nucleoside bases or their equivalents, Q and J are end groups useful in anti-sense oligomers and their use in affecting genetic material, e.g. as triplex or antisense in the treatment of disease.

...and stating the following:

At the Twelth American Peptide Symposium at the Massachusetts Institute of Technology in Cambridge, Massachusetts on June 17, 1991, Rolf Berg of the RISO
30 National Laboratory in Roiskilde, Denmark presented work on modified peptides with nucleoside side chains which were called peptide nucleic acids (PNAs). However, only PNAs from the T monomer could be made. Presentations by this

Our PCT: ”A” reduced to practice in 1992



PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07K 5/00, 7/00, C12Q 1/68
C08L 77/00

A1

(11) International Publication Number: WO 92/20702

(43) International Publication Date: 26 November 1992 (26.11.92)

(21) International Application Number: PCT/EP92/01219

(22) International Filing Date: 22 May 1992 (22.05.92)

(30) Priority data:

0986/91	24 May 1991 (24.05.91)	DK
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(57) Abstract

A novel class of compounds, known as peptide nucleic acids, bind complementary ssDNA and RNA strands more strongly than a corresponding DNA. The peptide nucleic acids generally comprise ligands such as naturally occurring DNA bases attached to a peptide backbone through a suitable linker.

THANKS!

Really appreciate your time!